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Operative Hemostasis in Trauma and Acute Care Surgery: The Role of Biosurgical Agents

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Abstract

Trauma and acute care surgery (TACS) constitutes the foundation of emergency surgical services in the United States. Blunt and penetrating traumatic injuries are a leading cause of death worldwide. Non-trauma general surgical emergencies are also a major source of morbidity and mortality. Operative interventions performed within the scope of TACS often revolve around the core principles of contamination control, hemostasis, surgical repair, and subsequent functional restoration. Hemorrhage control is an integral part of emergent operative interventions, and while most instances of surgical bleeding require direct suture ligation or some other form of direct tissue intervention, some circumstances call for the use of adjunctive means of hemostasis. This is especially applicable to situations and settings where direct applications of surgical energy, suture ligation, or direct compression are not possible. Difficult-to-control bleeding can be highly lethal and operative control can be very challenging when confounded by the lethal triad of acidosis, coagulopathy and hypothermia. Topical biosurgical materials (BSM) are of great value in such scenarios, and their use across a variety of settings, from pre-hospital trauma application to emergency general surgery operations, represents an important adjunct to improve patient outcomes. Here we present the different BSMs, discuss their various uses, and provide insight on future applications and developments in this important area.

Keywords: acute care surgery, biosurgical hemostatic agent, injury, operative interventions, patient outcomes, trauma

1. Introduction

Achieving and maintaining hemostasis is essential across all subspecialties of surgery [1–6]. Direct application of pressure, suture ligation, and electrocautery may sufficiently control bleeding during straightforward procedures, however, such methods are often ineffective in hemodynamically unstable, coagulopathic or septic patients [6–8]. Biosurgical hemostats are increasingly important in facilitating hemostasis when standard measures prove inadequate, or in situations such as prehospital trauma [7, 9]. Biosurgical materials (BSM) are available in cotton-like, powder, patch, liquid, and glue format, and are classified based on their properties and interactions within the coagulation cascade [5, 10, 11]. The goal of this chapter

is to review the many intricacies and molecular physiology of hemostasis, and to discuss the current role for biosurgicals within the overall operative strategy, focusing on applications of BSMs in acute care surgery and trauma.

2. Methods

The authors performed an exhaustive medical literature search utilizing PubMed and Google Scholar™ platforms. The following terms were utilized, alone or various combinations: “acute care surgery,” “biosurgical hemostat,” “biosurgical material,” “bleeding,” “coagulopathy,” “emergency surgery,” “hemorrhage,” “hemostasis,” “injury,” “management,” “non-surgical bleeding,” “surgery,” “transfusion,” “trauma.” Additional references identified during the primary literature search were subsequently reviewed and added. From more than 27,781,100 citations, we narrowed down the candidate study list to approximately 1400. The final reference list included the 90 results most relevant to the current chapter.

3. Coagulation cascade

The multiprotein coagulation cascade consists of two separate pathways, the contact mediated (intrinsic) and tissue factor (extrinsic) pathway which together unite to activate thrombin and form the fibrin plug (**Figure 1**) [12, 13]. Many of the anticoagulant medications focus on altering the steps herein, and the inherited coagulopathic disorders also feature abnormalities at various steps in the pathway [13, 14]. BSMs also interact here, as the so-called *active* agents contain thrombin and fibrinogen components, whereas *passive* agents rely on an already intact cascade [5].

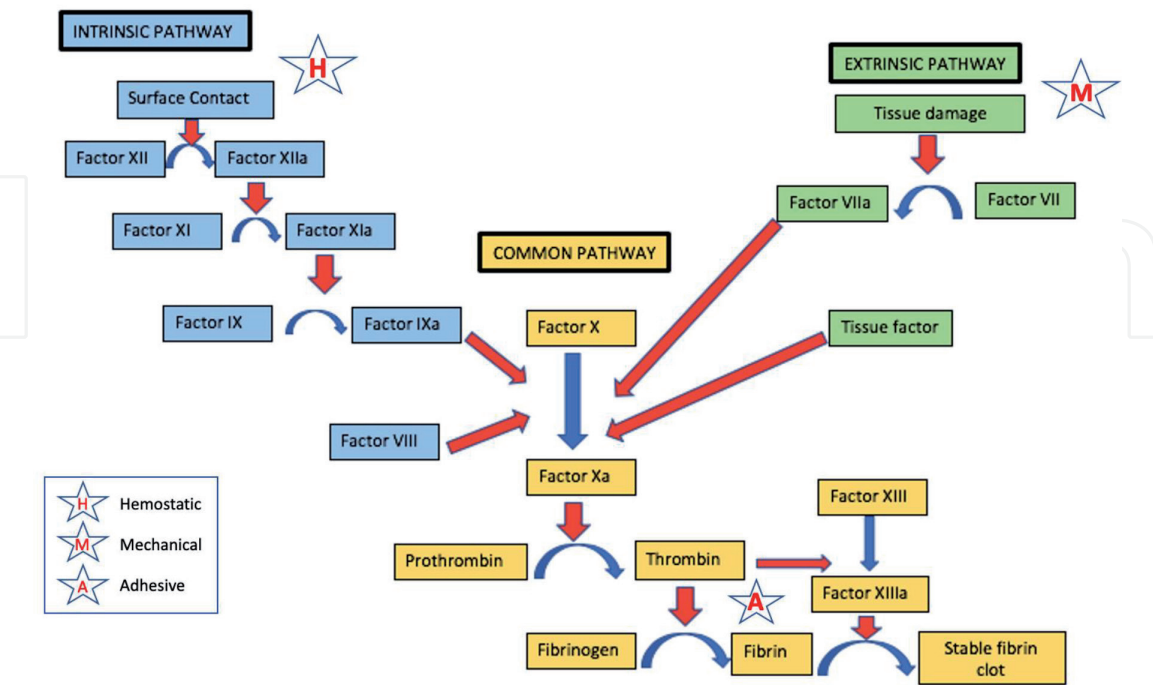


Figure 1. Overview of coagulation cascade. Diagram of the multistep intrinsic (left, blue) and extrinsic pathway (right, green). Whether initiated by surface contact or tissue damage, both pathways combine into the common pathway leading to activation of factor X and then subsequent thrombin-fibrin activation and finally formation of the fibrin clot. Legend demonstrates where hemostatic agents, mechanical, and adhesive hemostats exert their roles in the coagulation cascade.

4. Adhesive hemostats

Adhesive agents, whether liquid or fibrin patch, contain thrombin and fibrin thereby facilitating the final steps of the coagulation cascade [5, 11]. These added factors may help facilitate hemostasis in patients with various functional impairments within the coagulation cascade [15, 16]. Alterations within the coagulation mechanism that lead to the so-called “non-surgical bleeding” may be due to coagulopathy of massive traumatic hemorrhage, large intraoperative blood losses, or sepsis secondary to gastrointestinal perforation [8, 17–20]. Within the broader context of surgical “damage control” emerges perhaps the most compelling use case for BSMs [21, 22].

Historically, adhesive preparations contained additional antifibrinolytic components such as tranexamic acid (TXA) and aprotinin, which are no longer utilized due to reported side effects in cardiac surgery, including anaphylaxis, renal failure, increased mortality (aprotinin), and neurotoxicity (tranexamic acid) [23–25]. There are several liquid formulations of adhesive hemostats and “patch” alternatives available today (**Table 1**) [5]. Liquid adhesives are easily applied to delicate tissue, while fibrin patch alternatives can be more bluntly applied to brisk hemorrhage thereby providing improved hemostasis for various tissue types [5].

Adhesive				
Name	Manufacturer	Mechanism	Form	Comment
Beriplast	CSL Behring LLC King of Prussia, PA, USA	Thrombin/fibrin	Liquid	Hemostasis on native and PTFE surfaces
Evicel	Omrix LTD Ness Ziona, IL, USA	Thrombin/fibrin	Liquid	Hemostasis on native and PTFE anastomosis, help with dural suture lines
Floseal	Baxter Inc. Deerfeild, IL, USA	Thrombin/ fibrin+porcine gelatine	Liquid	
Qubeil	Omrix LTD Ness Ziona, IL, USA	Thrombin/fibrin	Liquid	
Surgiflo	J & J Healthcare Hacketstown, NJ, USA	Thrombin/ fibrin+porcine gelatin	Liquid	
Tisseal	Baxter Inc. Deerfeild, IL, USA	Thrombin/fibrin	Liquid	Hemostasis on native and PTFE surfaces
Evarrest	Omrix LTD Ness Ziona, IL USA	Thrombin/fibrin	Patch	Patch provides added compression
Tachosil	Baxter Inc. Deerfeild, IL USA	Thrombin/ fibrin+equine collagen patch	Patch	Patch provides added compression, hemostasis on portal and hepatic artery anastomosis
Use when coagulation cascade impaired. Do not use in the setting of allergy to blood products. Thromboembolic risk with intravascular administration				
Overview of adhesive hemostats name, manufacturer, mechanism, and form.				

Table 1.
Adhesive hemostats.

Among available products, different brands have their own unique fibrinogen/thrombin ratio affecting clot strength and drying time [5, 9, 26]. In general, higher thrombin concentrations correlate with the rate of clot formation whereas increased fibrinogen levels are associated with overall clot strength, which is not surprising as thrombin functions more proximally to fibrinogen, acting as a limiting reagent in the coagulation cascade, whereas fibrinogen more directly affects fibrin levels within the fibrin plug (**Figure 1**) [27–33].

Clinical trials focused on controlling intrabdominal and retroperitoneal hemorrhage have demonstrated that adhesive hemostats containing fibrin/thrombin coagulation factors tend to be superior to hemostats lacking these components [5]. A number of vascular surgery studies have shown significant improvement in the rate of hemostasis on native and polytetrafluoroethylene (PTFE) arterial anastomosis with several such agents (**Table 1**) [25, 34, 35]. In neurosurgical applications, another thrombin/fibrin adhesive was shown effective in helping to seal dural suture line leaks [36, 37]. For abdominal applications, one type of a hemostatic honeycomb patch matrix with added fibrin and thrombin factors was shown to reduce anastomotic bleeding following portal vein repair and hepatic artery reconstruction (**Table 1**) [5, 38]. However, there are conflicting data on whether these hemostatic agents can reduce the incidence of “structural” (versus “hemostatic”) events, such as postoperative pancreatic fistula following distal pancreatectomy, bile leakage status post hepatectomy, and persistent air leak after thoracic surgery [5].

5. Mechanical hemostats

Mechanical hemostats typically consist of cellulose, collagen, gelatin, and other plant-based materials [39–41]. The composition of these BSMs differs from the adhesive hemostats, as they lack coagulation factors and therefore require a functioning coagulation cascade to exert their effects [5]. Their mechanism of action relies on the absorbent capacity of the material, thereby exerting mass effect on the adjacent tissue and subsequent activation of the extrinsic coagulation pathway (**Figure 1**) [9, 42, 43].

6. Cellulose

Oxidized cellulose based hemostats are classified according to the way they are processed (regenerated versus non-regenerated) [5]. In short, the regenerated products have a more organized structure and conform better to their surroundings in comparison to the latter. Despite this, multiple studies have demonstrated greater hemostatic capacity for the non-regenerated products [44–46]. There are numerous products based on oxidized regenerated cellulose as the primary BSM, with relatively fewer non-regenerated products (**Table 2**) [5, 46]. In comparison to the adhesive hemostats, mechanical products are generally easier to use, relatively less expensive, and also exhibit bacteriostatic properties due to their low pH [20, 47–49]. Even though cellulose degrades within approximately 5 weeks, one limitation to its use includes the increased formation of granulation tissue months afterwards, which may produce a mass effect on vessels with subsequent stenosis or paralysis if adjacent nerves are compressed [50–54]. Moreover, the postoperative course for cancer patients may become significantly more complicated if granulation tissue results in a pseudotumor following the resection of the recurrent mass [50–55].

Mechanical				
Name	Manufacturer	Mechanism	Form	Comment
Surgicel	Ethicon Somerville, NJ, USA	Oxidized cellulose	Sheet	
Surgicel Fibrillar	Ethicon Somerville, NJ, USA	Oxidized cellulose	Sheet	
Surgicel Nu-kit	J & J Healthcare Hackettstown, NJ, USA	Oxidized cellulose	Sheet	
Traumastem	Bloster Veverská Bitýška, Czech Republic	Oxidized cellulose	Sheet	
Avitene	Bard Warwick, RI, USA	Collagen	Sheet/sponge/ powder	Hemostasis during crainiotomy
Gelfoam	Pfizer NY, NY, USA	porcine gelatin	Sponge	
Arista	Bard Warwick, RI, USA	polysaccharide spheres	Powder	Improved hemostatis in cardiothoracic surgery
Need normal coagulation cascade. Low pH with bacteriacidal properties. Thromboembolic risk with intravascular infection.				
Overview of mechanical hemostats name, manufacturer, mechanism, and form.				

Table 2.
Mechanical hemostats.

7. Collagen-based biosurgicals

Collagen is a key component of extracellular membranes and, as such, a great deal of effort has been placed into bioengineering collagen-based biosurgicals (CBBs) [56]. Additionally it is thought that such hemostats would also facilitate wound healing and potentially assist in neovascularization [56]. One CBB is known to improve perioperative hemostasis during craniotomy, and similar collagen based materials were shown to improve hemostasis during gynecological procedures (Table 2) [57, 58]. A recently bioengineered product containing cellulose, chitosan, and oxidized bacterial cellulose was shown to be both bactericidal and hemostatic in an animal model of liver injury, comparing favorably to a commonly used alternative [59].

8. Gelatin-based mechanical hemostats

Gelatin based mechanical hemostats which are either bovine- or porcine-based, have a neutral pH permitting combination with thrombin adhesives [60]. Therefore their hemostatic function extends into two domains, including both “absorptive-mediated” activation of the extrinsic pathway in addition to facilitating the final steps of the thrombin-fibrin cascade [5, 61]. In terms of biodegradation, gelatin sponge, granule, and powder dissolves within approximately 6 weeks of placement

[5]. Both gelatin- and collagen-based hemostats are effective in reducing perioperative blood loss. Additionally, neurosurgical models suggest that collagen-based products may be superior in controlling hemorrhage in spinal fusion procedures [62]. Although collagen- and gelatin-based products may be less expensive than fibrin products, one negative aspect is that when actively using blood saving techniques (e.g., cell-saver device), these products may pass through 20 micron filters leading to an inflammatory renal response [63].

Another mechanical hemostat category is derived from plant starch and is known as a microporous polysaccharide hemosphere (MPH) (**Table 2**) [64]. This highly absorbent product works similar to collagen and gelatin formulations through activation of the extrinsic clotting cascade. However, in comparison to collagen and gelatin, sufficient evidence exists in cardiothoracic surgery to demonstrate improved hemorrhage control, reduced chest tube output and fewer perioperative blood product transfusions [5]. From orthopedic surgery perspective, MPH may be favored as it does not inhibit bone healing compared to bone wax or microfibrillar collagen [65]. Moreover, microporous hemospheres absorb blood rapidly and have less capacity to cause infection and granuloma than other biologic hemostats [5, 66].

9. Sealant hemostats

Sealant hemostats (SH) are a class of hemostatic polymers which form a matrix by crosslinking and interlocking protein-rich adjacent tissues. Interestingly, sealants neither require the presence of blood products nor an intact coagulation cascade to exert their effects [5]. Natural sealants are derived from proteins and polysaccharides, while synthetic and semisynthetic products are composed of polyethylene glycol cyanoacrylate (PEG), polyurethane, dendrimer, and glutaraldehyde albumin biomaterials [67, 68]. Composite sealants contain both natural and synthetic components. All have been exploited for hemostasis, wound healing, fistula repair and implant fixation in fields such as cardiothoracic, biliary, urologic, plastic, neuro, and endoscopic surgery [68].

Natural fibrin based sealants are a mixture of fibrinogen and thrombin and come in either dry or foam preparations. They are mainly used to decrease suture and staple line seepage [56, 68]. Other proteins utilized in sealant applications include collagen, keratin, albumin, as well as muscle-derived products [68]. Polysaccharide compounds include chitosan, alginates, and chondroitin sulfates [69, 70]. A recent phase III clinical trial revealed that a fibrin-based sealant can provide excellent hemostasis, potentially superior to manual compression in patients undergoing open arterial surgery [71]. Interestingly, some of the well-known fibrin-based hemostats which leverage the coagulation cascade as the primary mechanism of action also exhibit a sealant function via covalent interactions with the surrounding tissues [56]. Even though fibrin sealants may be less effective in blood-saturated tissues, the potential benefit of an added “sealant feature” provided insight into research on new hemostatic sealants characterized by increased overall strength, elasticity, and stronger covalent interactions with surrounding tissues [72]. Other limitations of fibrin sealants include increased price compared to synthetic products, as well as high reliance on human plasma products for manufacturing purposes thereby increasing the risk, albeit very low, of transmissible disease [56].

PEG based products can be prepared in both patch and liquid formats to function as both hemostatic sealants and fluid barriers (**Table 3**) [5, 56]. There are patch products infused with collagen or cellulose, with superior hemostatic properties (**Table 3**) [5, 73]. Studies show less bleeding around anastomotic suture lines in

Sealants				
Name	Manufacturer	Mechanism	Form	Other
Hemopatch	Baxter Deerfield, IL, USA	PEG/collagen	Patch	Data to support use in nephrectomies and CABG
Duraseal	Integra Palmsboro township, NJ, uSA	PEG	Liquid	Improves dural closure
Veriset	Covidien Walpole, MA, USA	PEG/cellulose	Patch	Decreased bleeding after hepatectomy
FocalSeal	Focal Inc. Lexington, MA, USA	Eosin primer/PEG	Liquid	Decreased air leak after lobectomy
TissuGlu	Cohera Medical Oplotnica, Solvania	Polyurethane	Liquid	
Dermabond	Ethicon Somerville, NJ, USA	Cryanoacrylate	Liquid	Exothermic reaction
Bioglue	CryoLife Kennesaw, GA, USA	glutaraldehyde-bovine albumin	Liquid	Safe for vascular anastomosis
Do not use with renal disease patient's				
Overview of hemostatic sealants name, manufacturer, mechanism, and form.				

Table 3.
Hemostatic sealants.

nephrectomy and coronary artery bypass procedures with the use of bovine collagen and pentaerythritol polyethylene glycol ether tetra-succinimidyl glutarate patch [44, 46]. Similarly, a combined PEG and oxidized cellulose product significantly reduced oozing in hepatectomy procedures [74]. Another related product is effective as a fluid barrier and significantly improves closure of the dura during spinal surgery [75–77]. Finally, PEG-albumin sealants appear to be able to similarly reduce air leaks following pulmonary lobectomy procedures [44, 78, 79].

Polyurethane sealants have great potential and promise due to their highly elastic properties. Of importance, in an animal abdominoplasty model, this type of sealant was found to reduce seroma formation [56]. However there are safety concerns due to the potential thrombotic risk associated with similar products [56].

It is important to note that hemostatic sealants are not without risks, and their limitations include some concerns regarding the strength of the deployed material as well as some degree of interference with wound healing [68]. Although synthetic sealants have increased elasticity compared to natural counterparts, their limitations include longer curing time, the potential for chronic inflammation and the risk of cytotoxicity [56]. Moreover, PEG-based sealants should not be used in renal insufficiency as they are dependent on renal clearance following their breakdown and absorption [5]. Of note, PEG-sealants also tend to swell prior to degrading, which does provide tamponade assisting in hemostasis, but may be detrimental if applied within closed spaces that contain neurovascular structures or ureters [56]. Cyanoacrylates similar to those used in skin closure for improved cosmetic outcome, when used in large quantities, can produce significant amounts of heat and potentially lead to tissue damage [5]. Additionally, these products cannot be used intravascularly, or directly on vascular anastomoses, due to risk of embolization (in

fact, the material can be utilized in therapeutic embolization and other hemostatic maneuvers) [80–82]. The glutaraldehyde-bovine albumin, on the other hand, is safe and effective to directly apply on vascular and cardiac anastomotic suture sites [5]. Moreover, the use of this type of substance was shown to reduce blood transfusion requirements postoperatively, appears to be safe on adjacent nerves, and carries only a limited risk of vascular anastomotic stenosis secondary to an inflammatory response if the product is applied circumferentially [5].

10. Hemostatic dressings

Mineral-based and polysaccharide containing hemostatic dressings are of great value for pre-hospital exsanguinating patients, especially when protective measures such as tourniquet placement are not feasible due to the anatomical location of the wound [83, 84]. Such dressings are classified based on their mechanism of action, and include factor concentrators, muco-adhesives, or procoagulants [5]. Factor concentrators composed of volcanic or clay minerals such as zeolite and smectite act by concentrating protein components of blood thereby facilitating clot formation. The most commonly used factor concentrator is composed of zeolite beads which can be poured directly into a wound to expedite hemostasis (Table 4). One downside of this product is that it releases significant amounts of heat in a highly exothermic reaction. Consequently, care must be taken to use this preparation externally only, with applications limited to quantities “as little as necessary” to stop external bleeding [5]. Muco-adhesive products consist of the polymer chitosan, a chitin based product, which is derived from crustacean exoskeleton material [85]. Interestingly, chitosan has no intrinsic hemostatic ability, but its chemical charge is opposite to erythrocytes, thus promoting hemostasis [86, 87].

Procoagulant hemostats work by actively facilitating the coagulation cascade. One product, known as “combat gauze,” consists of surgical dressing coated with the mineral kaolin (Table 4) [88]. Kaolin is a nonreactive mineral that activates the intrinsic, contact-mediated clotting pathway when it comes in direct contact with damaged tissue [5]. The product is non-absorbable and must be removed after hemostasis is achieved, but does not create the exothermic reaction observed in factor concentrators. Baker and colleagues demonstrated that a novel fibrin-based sealant was equally effective when compared to “combat gauze” in a porcine model of both hepatic and femoral artery injury [89]. Similarly, this novel fibrin sealant was also shown to be superior other formulations in a similar swine model of splenic

Hemostatic				
Name	Manufacturer	Mechanism	Form	Other
Quick clot	Z-Medica LLC Wallingford, CT, USA	Zeolite beads	Guaze	Exothermic reaction. Needs to be removed from wound.
HemCon	Tricol Biomedical Portland, OR, USA	Chitin	Gauze	Exothermic reaction. Needs to be removed from wound.
Quick clot Combat Guaze	Z-Medica LLC Wallingford, CT, USA	Kaolin	Gauze	Exothermic reaction. Needs to be removed from wound.
Use externally for significant bleeding				
Overview of hemostatic agents separated by name, manufacturer, mechanism, and formulation.				

Table 4.
Hemostatic agents.

laceration [90]. Further studies are ongoing in this important and rapidly developing area of clinical investigation.

11. Future directions and conclusion

The ideal surgical hemostat should be biocompatible with its target tissues, safe, easy-to-use, and capable of providing rapid hemostasis. Importantly, BSMs should be able to operate under a broad range of conditions, possibly even when applied to actively bleeding or oozing surfaces, without being washed away or immediately losing their potency. Additionally, the optimal hemostat should have sufficient strength to hold the tissues in place to accomplish tamponade and assist in further healing. In the field of trauma and acute care surgery BSMs should maintain high levels of effectiveness for at least several hours, only act on the intended target tissues, should preferably be biodegradable, and should not impair wound healing. Affordability and ease of application are also important considerations. Future product development should also aim to incorporate, whenever possible, bactericidal properties. Moreover, novel materials may perform better if components like collagen are added to also assist in subsequent wound healing and maintenance of tissue integrity. Additionally, future research should aim to further understand the various tissue-specific effects of surgical hemostats, as well as their molecular and cellular interactions in order to individualize and optimize the resultant clinical outcomes.

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